Genomic profiling and biomarkers in Alzheimer's disease: use and limitations

Valentina Escott-Price and Lesley Jones*

MRC Centre for Neuropsychiatric Genetics and Genomics

Cardiff University

Cardiff CF24 4HQ, UK

*corresponding author

Biomarkers will be essential in identifying subjects with prodromal Alzheimer's disease, in stratifying people for treatment trials and for analysing data from such trials. In their position paper "A strategic research agenda to the biomarker-based diagnosis of prodromal Alzheimer's disease", Boccardi *et al.* [1] set out the evidence for Alzheimer's disease (AD) biomarkers using a framework developed in oncology. This comprehensive review of imaging and CSF biomarkers draws attention to the lack of common standards and clinical validation across different health systems and the subsequent impact on diagnosis and prognosis. Unless addressed this will limit the ability of the community to conduct appropriately powered clinical trials. They comment on the potential power to be gained from integrating multiple biomarkers - this power could be further augmented by including genetic risk scores.

The successful identification of dozens of risk loci associated with AD has changed our view of its pathobiology, but so far the impact on diagnosis, therapies or prevention is small. Genomic profiling, using polygenic risk scores – summing the genetic risks over 1000s of DNA variants associated with disease - is a promising tool for prediction of risk of future progression to AD in premanifest or early symptomatic individuals, as the genetic risk remains unchanged throughout an individual's lifetime. The area under the receiver operator characteristic curve (AUC) is the most widely accepted test of prediction accuracy for classifying diseased and unaffected individuals (see Box 1). The AUC statistic of a genomic profile for any disease has an upper limit dictated by heritability and disease prevalence[2]. High prediction accuracy through genomic profiling can be achieved for diseases with high heritability and low prevalence, though late onset AD is neither. Nevertheless prediction is possible in AD. The maximum AUC statistic prediction accuracy by genetic profiling in clinical samples is estimated at 82% (for a lifetime AD prevalence 2%), compared with 68.8% based upon *APOE*-e4 and *APOE*-e2 alleles alone[3,4]. The most recent study by Desikan et al, 2017[5] provided an

independent validation of the polygenic risk score approach, using survival analysis modelling, to integrate AD risk variants for quantifying age of onset. Both studies demonstrated a strong genetic component that can be useful in predicting and modifying AD risk and might be usefully added to the panels of imaging and CSF biomarkers to augment their predictive abilities.

The expectation is that in AD, as in cancer, comprehensive genomic profiling will be critical in choosing targeted therapies based on the patient's unique risk profile. Whilst the polygenic risk scoring outlined above is a promising approach, genomic profiling for AD is still in its infancy, and integration with other emerging biomarkers would aid diagnostic power[6]. The clinical value of current AD genomic profiling in matching patients to targeted therapies needs to be investigated: one way of assessing the potential of this approach would be to examine performance in stratifying response in previous clinical trials.

A caveat to this is that genetic information can be generated at any point and a clear distinction needs to be made between the use of genetics in exploring disease mechanisms and powering treatment trials versus estimating risk of future disease in individuals who are currently well before the age of disease risk. Genetic testing for Mendelian diseases in at risk subjects has been available for many years but in diseases with few interventions is often not taken up. In Huntington's disease only 10-20% of the at risk population take up testing to confirm their genetic risk[7]. Even in diseases with available interventions such as inherited forms of breast and colon cancer, such testing is not always taken up[8,9]. Care must be exercised in the presentation of genetics to predict who will get disease. In any individual we cannot currently give a precise risk estimate of AD susceptibility and shifting of diagnostic boundaries to include the currently well raises other ethical dilemmas[10]. Even if it were

theoretically possible people might well choose not to know their status for a late-life disease such as AD. Much work in the presentation of such risks has been carried out by clinicians and genetic counsellors in inherited diseases, guided by their patient populations, and this valuable experience can guide the use of genetic data in common diseases with a heritable component. In addition there are some future challenges for which we should prepare: the advent of clinical trials for premanifest at risk people and new effective treatments will inevitably bring people forward for genomic risk prediction. These issues require serious consideration by scientists and clinicians working in AD, particularly when presenting research findings to the public.

Conflicts of interest

The authors declare no conflicts of interest.

Funding source

There was no role for any funding source in the material presented in this article. The opinions presented are the authors' own.

References

1 Boccardi M, Gallo V, Yasui Y, *et al.* The biomarker-based diagnosis of Alzheimer's disease. 2-lessons from oncology. *Neurobiol Aging* 2017; **52**: 141–52.
2 Wray NR, Yang J, Goddard ME, Visscher PM. The genetic interpretation of area under the ROC curve in genomic profiling. *PLoS Genet* 2010; **6**: e1000864.
3 Escott-Price V, Sims R, Bannister C, *et al.* Common polygenic variation enhances risk prediction for Alzheimer's disease. *Brain* 2015; **138**: 3673–84.
4 Escott-Price V, Shoai M, Pither R, Williams J, Hardy J. Polygenic score prediction captures nearly all common genetic risk for Alzheimer's disease. *Neurobiol Aging* 2016; published online Aug. DOI:10.1016/j.neurobiolaging.2016.07.018.
5 Desikan RS, Fan CC, Wang Y, *et al.* Genetic assessment of age-associated Alzheimer disease risk: Development and validation of a polygenic hazard score. *PLoS Med* 2017; **14**: e1002258.
6 Hampel H, O'Bryant S, Lista JI, *et al.* PRECISION MEDICINE - The Golden Gate for Detection, Treatment and Prevention of Alzheimer's Disease. *J Prev Alzheimer's Dis* 2016.
7 Nance MA. Genetic counseling and testing for Huntington's disease: A historical review. *Am J Med Genet B Neuropsychiatr Genet* 2017; **174**: 75–92.

8 Ayme A, Viassolo V, Rapiti E, *et al.* Determinants of genetic counseling uptake and its impact on breast cancer outcome: a population-based study. *Breast Cancer Res Treat* 2014; **144**: 379–89.
9 Sharaf RN, Myer P, Stave CD, Diamond LC, Ladabaum U. Uptake of genetic testing by relatives of lynch syndrome probands: a systematic review. *Clin Gastroenterol Hepatol* 2013; **11**: 1093–100.
10 Milne R, Karlawish J. Expanding engagement with the ethical implications of changing definitions of Alzheimer's disease. *The Lancet Psychiatry* 2017; **4**: e6–7.

Box 1

Genomic profile is often understood as individual's unique measure which combines the effects of many associated genetic variants to predict risk of disease.

The polygenic score for an individual is based upon aggregation of AD risk alleles which this individual carries. Since the contribution of genetic variants to the disease risk is different, the individual risk score is calculated as sum of risk genetic variants weighted by their AD-related effect sizes. The genetic risk variants comprising the polygenic score, are pre-selected from large and powerful AD genome-wide studies, and capture those which are most associated with the disease.

The ability of the polygenic score distribution to distinguish those with disease from cognitively normal individuals is assessed using logistic regression analysis. As a result of the logistic regression analysis the prediction probability (value between 0 and 1) is provided for each individual. The quality of the prediction can be assessed looking at the proportions of correctly predicted cases and controls (sensitivity and specificity) in this sample. The AUC measure combines the sensitivity and specificity into one single metric, and reflects the overall prediction accuracy of the polygenic risk score based classification.